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Original Article

Comparison Of Amlodipine And Enalapril As First Line Agent In Treatment Of Hypertension In Children

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Abstract

Background: Systemic hypertension is an important condition in childhood, with an estimated global population prevalence of 1-2%. The public health significance of hypertension is based on observations that confirm a strong tracking of blood pressure levels from childhood to adolescence. Commonly used medications as first line in children include Angiotensin Converting Enzyme Inhibitors (ACEI) , Calcium Channel Blockers (CCB), and β Blockers. Adult clinical practice guidelines such as Joint National Committe-8 (JNC-8) have clear recommendations based on clinical trial evidence for the first line drug. However, in children there is lack of evidence for clear recommendations for the first line drug

Design: Double blinded Randomized control trial

Setting: The study was conducted in Indira Gandhi institute of child health , Bangalore from January 2016 to January 2017.

Participants :The study comprised of Children aged 3-18 years with hypertension.

Objectives : (1) Whether the hypertension was controlled with the drug used (2) Dose required for the control of hypertension (3) Duration needed for the control of hypertension(4) The need to use additional antihypertensive drugs to control hypertension. (5) Adverse drug reactions (ADR)

Results: The mean age at presentation was 9.23±0.35 years with males being 57.5 % and females being 42.5%. Renal cause of hypertension was the most common cause with nephrotic syndrome accounting for 46.25% and Acute Glomerulonephritis 42.5 %. Primary hypertension was seen 6.25%. Amlodipine controlled blood pressure in 97.5 % children and Enalapril in 92.5%.. The reduction in blood pressure were comparable at 24 , 48 and 72 hours. Mean dose required for control of blood pressure in Amlodipine group was 0.26±0.01mg/kg/day and Enalapril group was 0.25±0.01mg/kg/day. No adverse reactions was noted to either drug.

Conclusion: 1) Amlodipine and Enalapril are both efficacious in the control of Paediatric Hypertension and there is no statistically significant difference between the two groups in terms of Blood Pressure control.

2) Administration of Enalapril and Amlodipine was not associated with any adverse effects.

Keywords: Children; Hypertension; Amlodipine; Enalapril.

INTRODUCTION

Hypertension is an important condition in hospital practice. In majority of children with severe hypertension, the raised blood pressure constitutes an association or complication of an underlying disorder that is easily detectable. However, hypertension may manifest for the first time without obvious features of a renal or cardiovascular disorder.[1]Most children with sustained, severe or symptomatic hypertension have an underlying etiology and are at risk for acute and chronic complications. There is increasing evidence that essential hypertension tracks into adulthood resulting in considerable cardiovascular morbidity. [1]Hence, it becomes increasingly important to detect and interrupt development of childhood and adolescent hypertension to reduce long term ill effect of the disease. With increasing prevalence of pediatric hypertension, there has been a growing number of clinical studies performed that demonstrate the blood pressure (BP)-lowering effects of antihypertensives and the side effect profiles of these medications. This has led Food and Drug Administration (FDA) to label many hypertensive medications, presently used for adults, appropriate for treating children and adolescents[2]

First line medications commonly used in children include Angiotensin Converting Enzyme Inhibitors (ACEI) , calcium channel blockers (CCB), and β blockers. However, there is lack of evidence for clear recommendations for the first line drug. This has led to heterogeneity in the management of childhood hypertension as several classes of agents are being chosen. The present study analyses the results regarding antihypertensive efficacy and treatment safety of amlodipine and enalapril as first line drugs in the treatment of hypertension in children

MATERIAL AND METHODS

Study design: Double blind Randomized control trial.
Study duration: January 2016 to January 2017
Inclusion criteria: Children aged 3-18 years with hypertension

Exclusion criteria :
1. Children on treatment for hypertension
2. Children presenting with hypertensive crisis : Hypertensive emergency/urgency
3. Underlying contraindication to the use of drugs.

Measures of outcome:(1).Whether the hypertension was controlled with the drug used . (2) Dose required for the control of hypertension (3) Duration needed for the control of hypertension..(4).The need to use additional antihypertensive drugs to control hypertension. (5) Adverse drug reactions (ADR).

Children aged 3-18 years, diagnosed with hypertension were included in the study .Children already on treatment for hypertension and those with hypertensive crises and no underlying contraindication to the use of drugs were excluded. The study was approved by Institutional ethical committee. Informed consent was obtained from the parents before enrollment. History, examination findings, laboratory values were recorded in a prestructured predesigned, pretested proforma.

Blood pressure was measured by auscultatory method using a Diamond Mercury Free Sphygmomanometer, using a stethoscope placed over the brachial artery pulse, proximal and medial to the cubital fossa, and below the bottom edge of the cuff . The right arm BP was measured for consistency and comparison to standard tables. All 4 limb BP was recorded as a part of etiological

evaluation. If BP>95th centile, 3 recordings taken and average calculated. The interval between each of the 3 recordings was 10 minutes. Either SBP/DBP or both more than 95th centile was considered as hypertension. In order to avoid inter-observer bias, the same person recorded blood pressure in all the study The BP in children was expressed as a percentile of normative data for age, gender and height according to The Fourth Report of working group on Blood Pressure control in children, commissioned by the National Heart, Lung and Blood Institute of the National Institutes of Health of America.[3] Patients were randomized with intention to treat into 2 groups- A and B.

Underlying contraindications to the drugs were ruled out prior to drug administration. Renal function tests were done and GFR(Glomerular flitration rate) was calculated. GFR<30ml/min/1.73m2 was excluded from the study. Ultrasound abdomen and Doppler was done to rule out renal artery stenosis. Randomization done into groups with help of computer generated random number list. The patient as well the investigator were blinded to the allocation to drug groups. Group A received Amlodipine as the first line agent and group B received Enalapril as the first line agent, in incremental doses from minimal dose as per recommendations by : "The Fourth Report of working group on Blood Pressure control in children. The response to drug was assessed based on the dosage required to lower the BP and time taken for response. Blood pressure was measured at admission (0 hour), 12 hours, 24 hours, 48 hours, 36 hours and 72 hours. Response to the drug was defined as blood pressure reduction to less than 95th centile.Both drugs were started at initial dose as per protocol. BP monitored every 12 hourly. Both drugs were administered as tablets and given as OD/BD dosing. The increments in dose was done as per recommendations by the Fourth report. [3]. Control of BP was defined as BP recording <95th centile. Those children whose BP was controlled at lower doses were monitored every 12 hourly to look for any rebound increase in hypertension. If optimal response(BP control : <95th centile) was not achieved upon reaching the maximal dose, appropriate 2nd line antihypertensive, belonging to a different class of drug was added as per protocol at 72 hours. Possible adverse effects to drugs was noted at 10 mins, 6 hours, 24 hours and 48 hours. Adverse effects were managed appropriately .Etiology of hypertension was evaluated based on 1st and 2nd line investigations . Need for 2nd drug and control of BP at the end of 1 week studied .

Statistical analysis: Descriptive and inferential statistical analysis has been carried out in the present study. Independent sample t test has been used to compare quantitative variables across 2 categories. Chi-square test of association has been used to find the significance of study parameters on categorical scale between two or more groups.

Pearson Chi square test and Fisher's Exact t test has been used to find the association between two categorical variables. The stastical software namely IBM SPSS version 22 was used for analysis of te data and Microsoft word and excel have been used to generate graphs and table.

RESULTS:

A total of 109 patients were enrolled in the study out of which 29 were excluded. An informed consent was obtained .80 participants were then randomized into Amlodipine group (n=40) and Enalprilgroup(n=40). It is observed that in age group <8 years , there were 14 (35%)in Amlodipine group and 11 (27.5%) in the Enalapril group. 8-12 years, there were 22 (55%) in the Amlodipine group and 23(57.5%) in the Enalapril group. > 12 years, there were 4 (10%) in the Amlodipine group and 6 (15%) in the Enalapril group and there is no statistically siginificant difference (p value : 0.67) between Amlodipine and Enalapril study subjects in age distribution.The mean age of presentation was 9.23±0.35 years and hypertension was more common in the 8-12 years group (55%).

TABLE 1: SPECIFIC ETIOLOGY OF HYPERTENSION IN THE TWO GROUPS

SPECIFIC ETIOLOGY	GROUP A		GROUP B	
	NO.	%	NO.	%
NEPHROTIC SYNDROME	22	55	15	37.5
ACUTE GLOMERULONEPHRITIS	14	35	20	50
CHRONIC KIDNEY DISEASE	1	2.5	0	-
VASCULITIS SYNDROME	1	2.5	1	2.5
PRIMARY HYPERTENSION	2	5	3	7.5
ENDOCRINE CAUSES	-	-	1	2.5
TOTAL	40	100	40	100

Patient profile: In our study there were 21 males (52.5%) in the Amlodipine group and 25 (62.5%) in the Enalapril group. Above data suggests male sex predominates the sample group.There is no statistically siginificant difference (p value : 0.365) in sex distributuion among two groups. It was seen that 37 (92.5%) were renal causes for hypertension in Amlodpine group and 36 (90%) in the Enalapril group. This suggests that renal cause for hypertension was noted to be more common in the study population..It was noted that Nephrotic syndrome and Acute glomerulonephritis were the two most common causes. Nephrotic syndrome was seen in 22 (55%) in Amlodipine group and 15 (37.5%) in the Enalapril group. Acute glomerulonephritis accounted for 14 (35%) in the Amlodpine group and 20 (50%) in the Enalapril group. Chronic kidney disease was seen in 2.5% and 5% respectively. Vasculitis accounted for 2 cases (2.55%) in each group, both cases were evaluated and diagnosed as Systemic Lupus Erythematosus. One Endocrine cause was noted which was Cushing syndrome. Primary hypertension was seen in 5% in Amlodipine group and 7.5% in the Enalaprilgroup.

TABLE 2 : BASELINE CHARACTERISTICS IN THE STUDY GROUP

CHARACTERISTICS	AMLODIPINE (n=40)	ENALAPRIL(n=40)
MEAN AGE (YEARS)	8.7±0.38	9.5±0.57
SEX MALE (%) FEMALE(%)	52.5 47.5	62.5 37.5
STAGE OF HYPERTENSIONAT ADMISSION (%) STAGE 1 STAGE 2	 77.5 22.5	 62.5 37..5
ETIOLOGY (%)RENAL NON RENAL	2.5 7.5	90 10

In our study it was observed that 31 (77.5%) children in Amlodipine group and 25 (62.5%) in Enalapril group presented with Stage 1 hypertension. (p value:0.14). It can be seen that secondary causes for hypertension were more common than primary hypertension. Secondary hypertension accounted for 38 (95%) in the Amlodpine group and 37 (92.5%) in the Enalapril group. At the end of 12 hours, 10 (25%) children in the Amlodipine group had BP<95th centile and 22 (55%) children in the Enalapril group had BP<95th centile. At 48 hours, 4 of 10 patients receiving Enalapril, had their BP controlled [< 95th centile] and 9 of 12 patients receiving Amlodipine, had their BP controlled At 72 hours, 3 of 6 patients receiving Enalapril, 0.6 mg/Kg had their BP controlled [< 95th centile] and 2 of 3 patients receiving Amlodipine, 0.6 mg/Kg had their BP controlled. At the end of 72 hours, 3 children in the Enalapril group and 1 child in the Amlodipine group had BP>95th centile and hence 2nd line drug was added. In our study, out of 80 children, 3 children required 2 drugs for control of blood pressure : 2 in the Enalapril (diagnosed as IgM nephropathy) and 1 in the Amlodpine group(FSGS). One child in the Enalaprilgroup,required 3 drugs to control blood pressure, biopsy done in this child showed Lupus Nephritis. The above table shows that 55% children in Enalapril group responded at 12 hours, but 25% responded in Amlodipine group. This was statistically significant(p value : 0.006) Thus, Enalapril causes a faster reduction of blood

pressure than Amlodipine. The blood pressure reductions are comparable at 24, 48 and 72 hours.(p values not significant). Mean duration for control of blood pressure (<95th centile) was 26.15±2 hours. Mean duration for control of blood pressure was 21.72± 2.4 hour. The above table shows that at a dose of 0.2mg/kg, 28 (70%) children in the Amlodipine group and 30(75%) children in the Enalapril group had BP controlled.

TABLE 3 : DURATION TAKEN FOR RESPONSE

CHARACTERISTICS	AMLODIPINE(n=40)	ENALAPRIL(n=40)	P VALUE
RESPONSE RATE AT12 HOURS (%)	25	55	**0.006**
RESPONSE RATE AT24 HOURS (%)	60	44.5	0.29
RESPONSE RATE AT48 HOURS (%)	75	40	0.19
RESPONSE RATE AT72 HOURS (%)	60	44.5	0.29

9 (22.5%) children in the Amlodipine group and 4 (10%) children in the Enalapril group required 0.4mg/kg for control of BP. 2 (5%) children in the Amlodipine group and 3(7.5%) children in the Enalapril group required 0.6mg/kg for control of BP. Mean dose of Amlodipine needed for control of blood pressure was : 0.26±0.01mg/kg/day .Mean dose of Enalapril needed for control of blood pressure was : 0.25±0.01mg/kg/day. Response was comparable with both Amlodipine and Enalapril at lowest dose. 27.5% needed dose esclataion with Amlodipine and 17.5% with Enalapril. However, the difference was not statistically significant. 7.5% children did not respond even at maximum dose of Enalapril and 2.5% did not respond in Amlodipine group. The response rates of both amlodipine and enalapril were comparable for all causes of hypertension. Both drugs showed equal efficacy in primary hypertension. 95.4% cases of nephrotic syndrome attained control with amlodipine and 86.6% with enalapril. The cases of nephrotic syndrome who required 2nd line drug were Non-Minimal change nephrotic syndrome. One child in the enalapril group who was diagnosed as Lupus nephritis, did not attain BP control with maximum dose and hence needed addition of 2nd line drug. All children with Acute glomerulonephritis, Vasculitis, and primary hypertension attained BP control and 95.4% children with nephrotic syndrome attained BP control with amlodipine. All children with Acute glomerulonephritis, primary hypertension and Endocrine causes (Cushing syndrome) had BP controlled with Enalapril. 86.6% children with nephritic syndrome had their BP controlled. One child with Systemic lupus erythematosus needed 2nd line drug as BP remained >95th centile even with maximum dose of enalapril No adverse drug reactions were noted in both enalapril and amlodipine groups. more common in the study population

DISCUSSION

There has been an evolution in the treatment of hypertension in children and adolescents over the past decade. This has been prioritized due to the increasing number of children and adolescents being diagnosed with this condition. There has also been an increasing number of clinical trials performed and completed that demonstrate the blood pressure (BP)-lowering effects of antihypertensives and the side effect profiles of these medications, and that has led to FDA-labeling of many antihypertensive medications for use in children and adolescents. However, none of these trials has provided definitive data on the optimal first line agent for this patient population.[4]There are no sufficient number of head-to-head medication trials involving children and adolescents to guide the choice of therapy.[5]

In the present study, the antihypertensive efficacy and safety of Amlodipine and Enalapril as first-line antihypertensive drugs in hypertension, was studied. These two drugs were chosen as their pharmacokinetic properties are similar. Thiry nine out of 40 children achieved control of hypertension with administration of amlodipine as compared to 37 out of 40 who received enalapril. One child in the Amlodipine group and 3 children in the Enalapril group were not able to achieve blood pressure control at a maximum dose at the end of 72 hours and hence 2nd line drug was

added.In our study, mean age of presentation was 9.23±0.35 years and hypertension was more common in the 8-12 years group (56.5%). 31.5% children were <8 years and 12.55 children were >12 years and hypetension was seen more commonly in the males (57.5%) than females (42.5%). This is comparable to the study, by Kota et al[6] in which it was noted that hypertension in children was more common after the age of 6 years (42.9%) with a mean age of 8 ± 2.1 years and a male:female ratio of 89:12. (70% were males). Similar results of lower prevalence of hypertension in females (11.6%) was noted by Lone, et al.[7]

In our study ,renal cause for hypertension was noted to be the most common(92%) and among the renal causes, Nephrotic syndrome and AGN were the most common causes. Previous studies such as Kota et al. [6]and Mohan et al[8]showed similar results with renal parenchymal disease accounting for 73.3%.

The epidemiology of hypertension in childhood and adolescence is shifting owing to the worldwide obesity epidemic: hypertension is more frequent, and primary hypertension has become the predominant cause seen in the young. In our study 6.25% of children had primary hypertension. The incidence of essential hypertension in children varies from 1% to 45% in various hospital-based studies from developed countries.[7,8,9]A similar finding was also reported elsewhere in India; Chakrabortyet al.[10]found 17.12% prevalence of primary hypertension and Khan et al.[11]reported 10.44% . Like in adults, choice of antihypertensive agents can include ACEIs, angiotensin receptor antagonists (ARBs), calcium antagonists, beta-blockers and diuretics. A few placebo-controlled studies are available, but almost no study directly comparing the efficacy and safety of different antihypertensive drugs in children or adolescents. 50. A review of 27 pediatric studies by Simonetti et al.reports comparable BP reductions with ACEIs (10.7/8.1 mmHg), ARBs (10.5/6.9 mmHg) and calcium antagonists (9.3/7.2 mmHg)[12]

In our study, mean dose of amlodipine required for control of BP was 0.26±0.01mg/kg/day and mean duration for control of blood pressure (<95th centile) was 26.15±2 hours. One out for 40 children did not achieve blood pressure control. The cause of hypertension in that child was Nephrotic syndrome. This child needed addition of 2nd line drug and in view of sustained hypertension, renal biopsy was done which showed Non-Minimal change nephrotic syndrome (Focal segmental glomerulosclerosis). According to Tallianet al[13], the mean titrated dose required to control BP was 0.29±0.11 mg/kg per day for those <13 years, 0.26±0.11 mg/kg per day for those 13 years. According to John W. Rogan et al[14]. the mean initial dose of amlodpine used to initiate therapy was 0.2 (±0.01) mg/kg per day.According to Joseph T Flynn et. Al[15]who compared amlodipine with placebo for reduction in blood pressure ,Amlodipine produced significantly greater reductions in systolic BP than placebo.

In our study, mean dose of Enalpril required for control of BP was 0.25±0.01mg/kg/day and mean duration for control of blood pressure was 21.72± 2.4 hours. Three out of 40 children did not achieve blood pressure control. 2 children had non minimal change nephrotic syndrome and biopsy done showed IgM Nephropathy. One child had SLE; biopsy done showed Grade IV Lupus Nephritis. According to Thomas Wells et al(38)., Enalapril appears to be an effective and generally well-tolerated antihypertensive agent in children aged 6 to 16 years. An initial dose of 2.5 mg in children weighing < 50 kg and 5 mg in children weighing more than 50 kg (mean = 0.2 mg/kg/day). They noted the following adverse effects: dizziness, headaches, chest pain, hypotension, diarrhea, cough, dyspnea, pruritis, rash, and blurred vision. Adverse experiences were more frequent in patients receiving higher doses but resulted in discontinuation of enalapril in fewer than 3% of the study patients. None of the study patients developed angioedema, renal failure, or hyperkalemia. However, our study did not report any adverse effects.

In our study, Enalapril was noted to reduce blood pressure faster compared to Amlodipine at lower doses. 55% children achieved blood pressure control at 12 hours as compared to 25% in Amlodipine group. However, their efficacy was comparable at higher doses.

No adverse drug reactions were noted in either groups and hence both Amlodipine and Enalapril are safe in the treatment of hypertension in children.

CONCLUSION:

ACE inhibitors and Calcium channel blockers are both used as first line agents in treatment of hypertension in children. There are no comparative studies to establish efficacy of these two drugs. The present study shows that both Amlodipine and Enalapril are equally efficacious in the treatment of hypertension as first line agents. Though 2.5% children receiving Amlodipine and 7.5% children receiving Enalapril had uncontrolled blood pressure at 72 hours after treatment initiation, it was not statistically significant. Enalapril causes a faster reduction of blood pressure at lower doses (0.2mg/kg/day). However, at higher doses, both the drugs are equally efficacious in reducing blood pressure. Both drugs are equally efficacious in renal and non renal causes.. Both drugs have comparable mean doses and mean duration needed to achieve blood pressure control. Large scale studies are needed to support the above results and establish statistical significance There is no consensus regarding the best initial therapy for hypertension in children and adolescents; comparative trials are lacking in the pediatric population. A survey of pediatric nephrologists indicated that 47% considered ACE inhibitors to be first-line therapy, 37% chose calcium-channel blockers, 15.3% chose diuretics, and 6.6% chose beta-blockers. 3 However, no such evidence-based guidelines exist for children, again because no similar studies have yet been conducted with children. The result of this lack of clear guidelines for treatment of hypertensive children are the widely varying drug choices. Whether or not this lack of consensus is truly detrimental to the care of children with hypertension is unknown. As illustrated by the results of the many pediatric clinical trials of antihypertensive medications, all classes of hypertensive agents seem to be effective at reducing BP in children . The only way to determine whether a specific agent or class of agent has unique benefits in hypertensive children would be to conduct a large-scale, multi-center pediatric clinical trials.

LIMITATIONS OF STUDY:

1) Ambulatory blood pressure recordings were not taken
2) Drug levels were not monitored hence peak concentration of drug leading on to blood pressure control could not be determined.

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